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Alpha$_1$ antitrypsin deficiency due to M^{Malton}Z phenotype: case report and family study

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The association between premature development of emphysema and α_1 antitrypsin deficiency is well recognised.[1] By the technique of isoelectric focusing on polyacrilamide gel, over 30 different alleles of α_1 antitrypsin have been identified.[2] Only four of these—namely, Z, M^{Maduarte}, M^{null}, and M^{Malton}—produce grossly reduced levels of α_1 antitrypsin, with the subsequent risk of emphysema in homozygotes and heterozygotes. In practice, however, only the ZZ phenotype, with a frequency of 0.029%, is seen with any regularity.[3] We report the first case history and family study in Europe of α_1 antitrypsin deficiency due to the M^{Malton}Z phenotype.

Case history

The proband, a 71 year old retired salesman, presented initially in 1978 with a 10 year history of progressive breathlessness. He had been a moderately heavy smoker of 20 cigarettes a day before stopping 20 years previously. Spirometry showed that FEV$_1$ was 1.1 l (41% predicted) and forced vital capacity (FVC) 2.8 l (75% predicted), with no appreciable bronchodilator response.

He presented acutely three years later with cough, thirst, and general malaise. On examination he was dyspnoeic and dehydrated with signs of left sided pneumonia. Investigations showed: haemoglobin 9.1 g/l, erythrocyte sedimentation rate 139 mm in the first hour, blood urea 16.2 mmol/l, serum calcium 3.4 mmol/l, and albumin 31 g/l. On protein electrophoresis a reduced α_1 region was evident along with a paraprotein band. Quantitatively the serum IgA concentration was grossly raised, IgM 0.1 (normal 0.5–1.7) g/l, and IgG 1.6 (normal 5–16) g/l; and α_1 antitrypsin was reduced to 0.3 (normal 1.8–3.0) g/l with the M^{Malton}Z phenotype.

A chest radiograph showed features of emphysema, which was more noticeable in the lower zones, and left sided consolidation, which subsequently resolved. Spirometry showed FEV$_1$ to be 1.0 l (45% predicted) and FVC 1.95 l (59% predicted). Carbon monoxide gas transfer was 13.5 ml^{-1} min^{-1} mm Hg^{-1} (4.5 mmol min^{-1} kPa^{-1}) (64% predicted) and a flow-volume loop had a concave expiratory phase compatible with emphysema.

The diagnosis of myelomatosis was confirmed. Treatment with standard doses of melphalan and intermittent prednisolone reduced the paraprotein concentration to 19% of its original value. Apart from moderate shortness of breath and recent backache after collapse of a lumbar vertebra, he remains symptom free.

Family study

All available members of the proband's family had a history taken and were examined clinically. None of the family had evidence of serious illness and physical examination showed nothing abnormal. Pulmonary function tests were performed and blood was sampled for α_1 antitrypsin concentration and phenotyping.

METHODS

Lung volumes were determined by helium dilution; FEV$_1$ and FVC were measured with the Vitalograph dry wedge spirometer; and carbon monoxide gas transfer was measured by the single breath method. Concentrations of α_1 antitrypsin were measured by automated immunological methods. Phenotyping was performed by polyacrilamide gel electrophoresis with isoelectric focusing, the M^{Malton} allele

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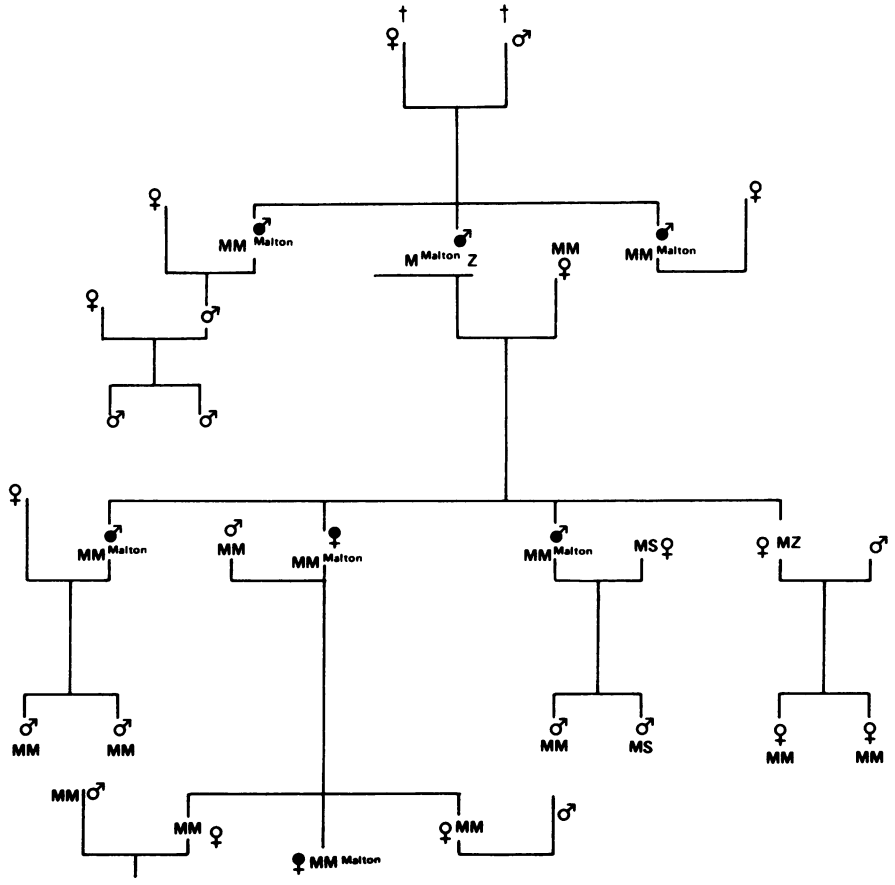
Table *Serum α_1 antitrypsin (AAT) concentration, alleles, and results of pulmonary function tests (expressed as percentages of predicted normal values)*

Relationship to proband	*Age (y)*	*Smoking*	*ATT* (g/l)*	*Pi*	*FEV$_1$*	*FVC*	*FEV$_1$/VC*	*TLCO*
Proband	71	Ex	0.3	M^{Malton}Z	45†	57‡	77‡	64†
Brother	73	+	1.2	MM^{Malton}	127	109	89	104
Brother	69	Ex	1.3	MM^{Malton}	100	112	117	116
Son	46	–	0.8	MM^{Malton}	100	90	100	88
Daughter	45	–	0.9	MM^{Malton}	120	120	119	115
Son	39	+	0.9	MM^{Malton}	114	117	106	132
Grandaughter	17	+	1.0	MM^{Malton}	120	116	112	95

*Normal range 1.8–3.0 g/l.
†Below 1 standard deviation from the mean.
‡Below 2 standard deviations from the mean (Cotes).[4]
FVC—forced vital capacity; TLCO—transfer factor for carbon monoxide.



Family tree showing carriers of the M^{Malton} allele (closed symbols). Where no phenotype is shown blood samples were not available.

being identified by virtue of its location between the N and P alleles.[2]

Results

Eighteen members of the family, excluding the proband, were studied. Ten had the MM phenotype with a mean α_1 antitrypsin concentration of 1.86 (range 1.4–2.7) g/l. One subject was phenotypically MS (α_1 antitrypsin concentration 1.6 g/l) and another MZ (α_1 antitrypsin concentration 1.2 g/l). The details of the remaining six subjects are shown in the table. The proband had abnormal pulmonary function but all of his six relations who were phenotypically MM^{Malton} had reduced α_1 antitrypsin concentrations (mean 1.07 g/l) with normal pulmonary function.

The family pedigree (figure) shows the M^{Malton} allele with a clear three generation transmission through the proband's daughter. No phenotypes are available for the children of the proband's brother.

Discussion

We have reported the first case in Europe of the M^{Malton} allele. In the original description[5] a 2 year old girl with a low α_1 antitrypsin concentration and a unique electrophoretic strip was subsequently phenotyped M^{Malton}Z, after the family name. Investigation of relatives defined a cousin also as Pi M^{Malton}Z, both her father and her aunt being Pi M^{Malton} and α_1 antitrypsin concentrations being 11–13% of the predicted normal. All had normal hepatic function and no history suggestive of emphysema, but they were below 30 years of age.

The second study published in English, that of Sproule and colleagues,[6] included four patients who were Pi M^{Malton}Z, their mean age being 37 years. All were smokers with clinical features of emphysema and reduced α_1 antitrypsin concentrations (mean 16.4% predicted). Pulmonary function tests indicated airflow obstruction (FEV_1 49.5% and FEV_1/FVC 44.3% of predicted values), increased total

lung capacity, and reduced gas transfer. Thirteen MM^{Malton} heterozygotes were discovered (mean α_1 antitrypsin concentration 66.5% predicted), five of whom smoked. Pulmonary function in these five and in two smokers with Pi MZ and intermediate α_1 antitrypsin concentrations was reported as having "a significant decrement in a number of measures of expiratory flow." Sproule and colleagues concluded that there was evidence of a detrimental effect of cigarette smoke in those individuals with a reduced circulating concentration of α_1 antitrypsin.

If their data are re-examined, however, this conclusion is surprising. FEV_1 in 14 Pi MM smokers was 98.5% (SD 18.9%) and in five MM^{Malton} smokers 95.8% (10.3%) of predicted normal. The difference in mean FEV_1 values between the two groups is not significant and in addition the MM^{Malton} heterozygotes had a mean age nine years greater and were heavier smokers.

In conclusion, we have confirmed the association between Pi $M^{Malton}Z$ and the high risk of developing emphysema. The results of our small family study of six MM^{Malton} heterozygotes, which included three smokers, two non-smokers, and one ex-smoker, in contrast to those of the study by Sproules *et al* produced no evidence to suggest that smokers with intermediate concentrations of α_1 antitrypsin due to the MM^{Malton} phenotype have a greater risk of developing emphysema than smokers with normal concentrations. This is in agreement with comparable studies in MZ heterozygotes.[7]

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Book notices

Ventilation/Blood Flow and Gas Exchange. 4th ed. JB West. (Pp 119; £6.50.) Oxford: Blackwell Scientific Publications, 1985.

Since it first appeared in 1965 this small book has been essential reading for all who need to understand gas exchange in the lung. It has performed its function so well that it is entirely appropriate that most of the recently issued fourth edition is identical word for word to the original version. There is a new chapter on distribution of ventilation-perfusion ratios, in which a previously theoretical concept is brought to life in a presentation of the results of the multiple inert gas elimination technique. This brings added interest and excitement to the subject, which will certainly benefit new owners of the book; but existing owners (this is not a book to borrow) need feel no urge to exchange their cherished earlier editions.—RALB

The Essentials of Respiratory Therapy. 2nd ed. RM Kacmarek, CW Mack, S Dimas. (Pp 632; £33.50.) Chicago: Year Book Medical Publishers Inc, 1985. ISBN 0-8151-4955-7.

This densely packed book is intended to be a summary of all the knowledge required by respiratory therapists, presented in numbered note form. It contains chapters on basic chemistry and physics (29 pages) and cardiological medicine, including fluid balance (114 pages); this is followed by chapters on gas therapy, oxygen therapy, airway care, aerosol therapy, chest physiotherapy, mechanical ventilation, analysers, more theory about fluid flow, microbiology, and the techniques of sterilisation. The book is designed for revision and for the preparation of lectures rather than for a first attack on these subjects. For example, the section on oxygen delivery systems does not describe the various masks but merely explains the ways of giving high and low flow systems and their relative advantages. There is a lot of technical information that would be hard to find elsewhere and some homespun advice: for example, how to wean a patient off a ventilator (in some detail). This is a specialised book for a particular audience and cannot be recommended for other professionals. A large intensive care ward with a major teaching commitment might find a use for some of the technical details contained in it, but I doubt if many would find the presentation congenial.—GL